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(19)

(54) A PROCESS FOR THE MANUFACTURE OF POLYENE COMPOUNDS

(71) We, F. HOFFMANN - LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do

hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for the manufacture of polyene compounds. More particularly, the invention is concerned with a process for the manufacture of polyene compounds containing a 3,7 - dimethyl - nona-1,3,5,7 - tetraen - 1 - yl group by reacting triarylphosphonium salts, preferably triphenylphosphonium salts, with aldehydes.

A process of the foregoing type (e.g. as used in the manufacture of vitamin A acetate by reacting a β-ionylidenethyltriphenylphosphonium halide with γ-acetoxytiglic aldehyde) has hitherto been carried out in an homogeneous phase using, for example, dimethylformamide, acetonitrile, acetone, dioxan or isopropanol as the solvent. Various disadvantages are encountered when the process is carried out in this manner. In particular, in order to obtain yields which are reasonably satisfactory, the reaction must be carried out at a very low temperature (i.e. at a temperature of below +5°C to about −30°C), which requires a substantial cooling capacity. If the reaction is carried out at a temperature greater than +5°C, the yield of end product (e.g. of vitamin A acetate) is considerably reduced (e.g. to about 80%). Furthermore, the proportion of cis-isomers in the end product is relatively high.

It has now been found in accordance with this invention that the aforementioned disadvantages of the known process for the manufacture of polyene compounds carrying a 3,7 - dimethyl - nona - 1,3,5,7 - tetraen-1 - group and also further disadvantages connected with this process can be eliminated by carrying out the reaction in a two phase, aqueous-organic solvent system, the organic phase consisting of an optionally chlorinated hydrocarbon which is immiscible with water and the volume ratio between the organic phase and water being between 10:1 and 1:20.

The present invention is based on the foregoing finding and is accordingly concerned with a process for the manufacture of polyene compounds containing a 3,7 - dimethyl-nona - 1,3,5,7 - tetraen - 1 - yl radical by reacting triarylphosphonium salts, preferably triphenylphosphonium salts, with aldehydes, which process comprises carrying out the reaction in a two phase, aqueous-organic solvent system, the organic phase consisting of an optionally chlorinated hydrocarbon which is immiscible with water and the volume ratio between the organic phase and water being 10:1 to 1:20.

In the foregoing manner it is possible to avoid the use of very low temperatures during the reaction. The reaction can therefore also be carried out at a temperature of greater than, for example, +5°C, without low yields being obtained. Even at temperatures up to 100°C, yields of 93% and more are still achieved.

Furthermore, by using the present process, in particular by applying it to a C_5+C_{15} vitamin A synthesis and in particular using excess water, the content of the desired trans-isomers is substantially higher whilst the formation of 9-cis-isomers is simultaneously extensively suppressed. In this manner, if the present process is applied to the manufacture of vitamin A acetate, all-trans-vitamin A acetate is predominantly obtained. The ratio

of all-trans to 11-cis is, for example, about 2.3 to 0°C, whilst this ratio is only 1.2 at −20°C when the reaction is carried out homogeneously.

Furthermore, in carrying out the present process, the flow of heat from the reaction mixture is less problematic, since one of the components of the solvent system is water. Because of the unproblematic flow of heat, it is also possible to carry out the reaction using high concentrations of the reactants.

It is also of advantage that the reaction mixture obtained according to the present process can be isomerised by customary methods, the all-trans-isomer being obtained in crystalline form in a simple manner.

A further advantage of the present process consists in that relatively cheap bases (e.g. sodium hydroxide solution) can be used as the bases required in the reaction.

Within the limits between 10:1 and 1:20, the volume ratio between the organic phase and water depends on the type of reactants, the concentration, the rate of stirring and the temperature.

The volume ratio between the organic phase and water is appropriately 1:1 to 1:10, preferably 5:1 to 1:5. According to a particularly preferred embodiment of the present process, an aqueous-organic solvent system is used in which water is present in excess; for example, a solvent system in which the volume ratio between the organic phase and water is about 1:4.

The organic phase of the aqueous-organic solvent system is conveniently an aromatic hydrocarbon (e.g. benzene or toluene) or, preferably, a chlorinated hydrocarbon, especially methylene chloride, ethylene chloride or chlorobenzene. Methylene chloride is particularly preferred. It is essential that the organic solvent is immiscible with water.

The present reaction can be carried out at a temperature between −10°C and +100°C, it being expedient to use a temperature between 0°C and +60°C, preferably a temperature between 0°C and +30°C.

Depending on the temperature used and the purity of the triarylphosphonium salt used, the reaction time can vary within wide limits; for example, between 2 minutes and 120 minutes.

It is known that the presence of bases is required for the reaction of a triarylphosphonium salt with an aldehyde. In the present process, inorganic bases, for example alkali metal hydroxides and alkaline earth metal hydroxides, preferably sodium hydroxide and potassium hydroxide, or substances having a basic reaction, for example metal carbonates (e.g. potassium carbonate) or ammonia or organic amines, preferably tertiary organic amines (e.g. trialkylamines such as triethylamine), are conveniently used. It has proved particularly convenient to add the base (e.g. aqueous sodium hydroxide solution) slowly dropwise to the reaction mixture so that always only a small concentration thereof prevails, and the pH value should be in the range between 8 and 12.

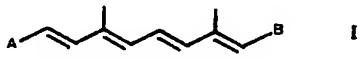
The customary triarylphosphonium salts (e.g. halides, for example the chloride, or the hydrogen sulphate) can be used as β-ionylidenethyltriphenylphosphonium salts.

The reaction is conveniently carried out under the atmosphere of an inert gas (e.g. argon) and with protection against light.

Furthermore, it has proved to be expedient to add to the reaction mixture an antioxidant (e.g. butylated hydroxytoluene or butylated hydroxyanisole).

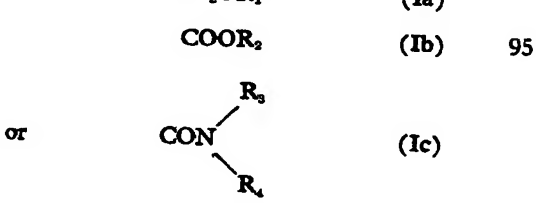
The present process can be carried out both batchwise and continuously.

Examples of polyene compounds, containing a 3,7 - dimethyl - nona - 1,3,5,7 - tetraen-1 - yl group, which can be manufactured by the present process are compounds of the general formula



I

wherein A represents the 2,6,6 - trimethyl-cyclohex - 1 - enyl group or a substituted phenyl group and B represents a group of the general formula



wherein R_1 represents an alkanoyl group, R_2 represents an alkyl group and R_3 and R_4 each represent a hydrogen atom or a lower alkyl group.

In formula Ia, R_1 represents an alkanoyl group, preferably one containing up to 18 carbon atoms (e.g. the acetyl, propionyl, butyryl, valeroyl, caproyl or palmitoyl group). A preferred alkanoyl group is the acetyl group.

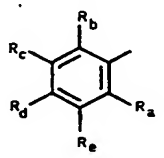
R_2 in formula Ib represents an alkyl group, preferably one containing up to 10 carbon atoms (e.g. the methyl, ethyl, propyl, isopropyl, butyl, pentyl or decyl group). In an especially preferred aspect, R_2 represents the methyl or the ethyl group.

In formula Ic, R_3 and R_4 can each represent a hydrogen atom or a lower alkyl group (i.e. an alkyl group containing up to 7 carbon atoms) for example the methyl, ethyl, propyl, isopropyl or heptyl group. The methyl group and the ethyl group are the preferred lower alkyl groups.

If A in formula I represents the 2,6,6-

trimethylcyclohex - 1 - enyl group the compounds of formula I are derivatives of vitamin A alcohol and vitamin A acid. The manufacture of these compounds, in particular the manufacture of vitamin A acetate, is particularly preferred.

Examples of substituted phenyl groups represented by A are groups of the general formula

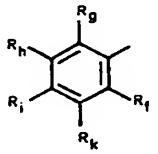


Id

wherein R_a and R_b each represent a lower alkyl group, R_c represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl) amino, di(lower alkyl)amino, lower alkanoylamido or N-heterocyclic group, R_d represents a hydrogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di-lower alkyl)amino, lower alkanoylamido or N-heterocyclic group and R_e represents a hydrogen or halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di-(lower alkyl)amino, lower alkanoylamido or N-heterocyclic group with the proviso that at least one of R_c, R_d and R_e represents other than a hydrogen atom and, when R_c or R_e represents a halogen atom, then R_d represents other than a lower alkoxy group.

Compounds of formula I in which A represents a substituted phenyl group of formula Id include 9 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraene - 1 acid ethyl ester and 9 - (4-methoxy - 2,3,6 - trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraene - 1 acid ethylamine. These compounds are described, for example, in Dutch Patent Application No. 7404324.

Further examples of substituted phenyl groups represented by A are group of the general formula

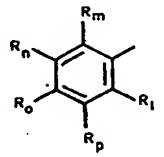


Ie

wherein one of the symbol pairs R_f and R_k, R_g and R_h, R_h and R_i or R_i and R_k are linked together to form a trimethylene, tetramethylene, 1,3-butadienylene, oxytrimethylene or 3-oxypropenylene ring, said rings being optionally substituted by one or more lower alkyl groups, and the remaining symbols each represent a hydrogen or halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino or N-heterocyclic group with the proviso that at least one of said symbols represents other than a hydrogen atom.

Examples of these compounds are 9 - (4,6-dimethyl - indan - 5 - yl) - 3,7 - dimethyl-nona - 2,4,6,8 - tetraene - 1 acid ethyl ester, 9 - (4 - methoxy - 2,3 - dimethyl - naphthalen - 5 - yl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraene - 1 acid ethyl ester and 9 - (5,7,8-trimethylchromen - 6 - yl) - 3,7 - dimethyl-nona 2,4,6,8 - tetraene - 1 acid methyl ester, which are described in Belgian Patent Specification No. 818648.

A third group of examples of substituted phenyl groups represented by A are groups of the general formula



If

wherein one of R_l and R_m represents a halogen atom or a lower alkyl group and the other represents a halogen atom or a lower alkoxy group, R_n and R_p each represent a hydrogen or halogen atom or a lower alkyl group with the proviso that one of R_n and R_p represents other than a halogen atom, and R_o represents a halogen atom or a lower alkoxy, amino, mono(lower alkyl)amino or di(lower alkyl)-amino group.

Examples of these compounds are 9 - (2-chloro - 4 - methoxy - 3,5,6 - trimethylphenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraene - 1 - acid ethyl ester and 9 - (2,6-dichloro - 4 - methoxy - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraene - 1 acid ethyl ester.

The synthesis of the polyene compounds which can be manufactured by the present invention can be carried out in a variety of ways depending on the number of carbon atoms which are contained in the triarylphosphonium salt and aldehyde reaction components. In the manufacture of vitamin A derivatives, that is to say of compounds of formula I in which A represents the 2,6,6-trimethyl - cyclohex - 1 - enyl group, the reaction can be carried out, for example, according to the procedure $C_{15} + C_5$, $C_{10} + C_{10}$ or $C_{15} + C_7$, it being particularly advantageous to use the $C_{15}+C_5$ procedure; for example, the reaction of a C_{15}-triarylphosphonium salt with a C_5-aldehyde.

In the manufacture of vitamin A acetate under the conditions of the present process, it has proved to be particularly advantageous to react a β-ionylidenethyltriphenylphosphonium salt, preferably a β-ionylidenethyltriphenyl-

phosphonium salt (e.g. the chloride or hydrogen sulphate), with γ-acetoxytiglic aldehyde.

The following Examples illustrate the present invention:

Example 1.

15 g of β-ionylidenethyltriphenylphosphonium chloride, 4.5 g of γ-acetoxytiglic aldehyde and 80 mg of butylated hydroxytoluene are suspended in 5 ml of methylene chloride at room temperature. 40 ml of water are then added to the suspension, after which 1.9 g of potassium hydroxide dissolved in 10 ml of water are added over a period of 16 minutes, whilst stirring vigorously After completion of the addition of the potassium hydroxide solution, the mixture is stirred for a further 15 minutes. The methylene chloride phase is then separated off and washed with 100 ml of water until neutral. The methylene chloride is then evaporated off and the mixture is distributed between methanol/water and hexane. After evaporation of the hexane, 9.84 g (100%) of a mixture of vitamin A acetate isomers having the following composition are obtained:

11,13-di-cis-vitamin A acetate	0.4%
11-cis-vitamin A acetate	35.7%
13-cis-vitamin A acetate	0.3%
9-cis-vitamin A acetate	0.5%
all-trans-vitamin A acetate	61.2%

The following Table summarises the results of experiments which were carried out under various reaction conditions (temperature and ratio between water and organic phase).

TABLE

Parts of H_2O	Parts of CH_2Cl_2	Temperature (°C)	9-cis %	11-cis %	all-trans %
1	1	0	2	38	59
8	1	0	<0.4	28	72
5	1	0		31	69
8	1	20		36	61

In all of these experiments the total yield was between 95% and 100%.

Example 2.

15 g of β-ionylidenethyltriphenylphosphonium chloride and 4.5 g of γ-acetoxytiglic aldehyde are added to a mixture of 40 ml of water and 10 ml of methylene chloride in a 100 ml 4-necked flask which is in an ice-bath and is provided with a stirrer, thermometer and dropping funnel at 0°C and under an atmosphere of argon. 1.87 g of potassium hydroxide dissolved in 10 ml of water are added dropwise to the mixture obtained over a period of 15 minutes whilst stirring. After completion of the addition of the potassium hydroxide solution, the mixture is stirred for a further 15 minutes. It is then neutralised with 1 ml of 2-N acetic acid, placed in a separating funnel and 100 ml of methanol are added and the mixture is subsequently extracted by shaking three times with 100 ml of hexane each time. The combined hexane phases are washed with 50 ml of methanol/water (80:20). The hexane phases are then dried and evaporated under reduced pressure for about 1 hour. 9.54 g (97%) of vitamin A acetate having the following isomer composition are obtained:

11-cis-vitamin A acetate	36.5%
9-cis-vitamin A acetate	0.7%
all-trans-vitamin A acetate	62.9%

Example 3.

The process was carried out in an analogous manner to that described in Example 2, but 80 ml of water and 5 ml of methylene chloride were used as the solvent system. 9.68 g (98.4%) of a vitamin A acetate isomer mixture having the following composition were obtained: 9-cis: 0.4%, 11-cis: 32.5% and all-trans: 66.3%.

Example 4.

The process was carried out in an analogous manner to that described in Example 2, but, in place of 15 g of β-ionylidenethyltriphenylphosphonium hydrogen sulphate were used and in place of 1.87 g of potassium hydroxide, 7.5 g of potassium carbonate were used. After adding the aqueous (10 ml of water) potassium carbonate solution over a period of 10 minutes, the mixture was stirred for a further 1 hour. 9.69 g (98.5%) of a vitamin A acetate isomer mixture having the following composition were obtained: 9-cis: 0.4%; 11-cis: 35.5% and all-trans: 62.5%.

Example 5.

19 g of β-ionylidenetriphenylphosphonium chloride and 7 g of 6 - acetoxy - 4 - methyl-hexa - 2,4 - dien - 1 - al are added to 40 ml of water and 10 ml of methylene chloride at 0°C. 2.69 g of potassium hydroxide dissolved in 7 ml of water are added to the resulting mixture over a period of 10 minutes whilst stirring and the mixture is then stirred for a further 1 hour at 0°C. After working up the mixture according to the foregoing Examples, 12.7 g (97%) of vitamin A acetate having the following isomer composition are obtained: 9-cis: 53%; all-trans: 45%.

Example 6.

10.54 g of 5 - (4 - methoxy - 2,3,6 - trimethyl - phenyl) - 3 - methyl - penta - 2,4-diene - 1 - triphenylphosphonium chloride and 2.84 g of hydroxysenecioic acid ethyl ester are added to 5 ml of methylene chloride and 20 ml of water at 0°C. 1.34 g of potassium hydroxide dissolved in 3 ml of water are added dropwise over a period of 15 minutes whilst stirring and the mixture is stirred for a further 1 hour at 0°C. After working up the mixture according to the foregoing Examples, 6.9 g (98%) of 9 - (4 - methoxy-2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl-nona - 2,4,6,8 - tetraene - 1 - acid ethyl ester containing 51% of the 11-cis-isomer and 47.4% of the all-trans-isomer are obtained.

WHAT WE CLAIM IS:—

1. A process for the manufacture of polyene compounds containing a 3,7 - dimethyl - nona-1,3,5,7 - tetraen - 5 - yl group by reacting triarylphosphonium salts with aldehydes, which process comprises carrying out the reaction in a two phase, aqueous-organic solvent system, the organic phase consisting of an optionally chlorinated hydrocarbon which is immiscible with water and the volume ratio between the organic phase and water being between 10:1 and 1:20.

2. A process according to claim 1, wherein the triarylphosphonium salts are triphenylphosphonium salts.

3. A process according to claim 1 or claim 2, wherein the volume ratio between the organic phase and water is 1:1 to 1:10.

4. A process according to any one of claims 1 to 3 inclusive, wherein the volume ratio between the organic phase and water is 1:1 to 1.5.

5. A process according to any one of claims 1 to 4 inclusive, wherein the volume ratio between the organic phase and water is about 1:4.

6. A process according to any one of claims 1 to 5 inclusive, wherein the organic phase of the aqueous-organic solvent system is a chlorinated hydrocarbon.

7. A process according to claim 6, wherein the chlorinated hydrocarbon is methylene chloride, ethylene chloride or chlorobenzene.

8. A process according to any one of claims 1 to 7 inclusive, wherein the reaction is carried out at a temperature between −10°C and +100°C.

9. A process according to any one of claims 1 to 8 inclusive, wherein the reaction is carried out at a temperature between 0°C and +60°C.

10. A process according to any one of claims 1 to 9 inclusive, wherein the reaction is carried out at a temperature between 0°C and +30°C.

11. A process according to any one of claims 1 to 10 inclusive for the manufacture of vitamin A acetate, which process comprises reacting a β-ionylidenethyltriarylphosphonium salt with γ-acetoxytiglic aldehyde.

12. A process according to claim 11, wherein the β - ionylidenethyltriarylphosphonium salt is a β-ionylidenethyltriphenylphosphonium salt.

13. A process according to claim 12, wherein the β-ionylidenethyltriphenylphosphonium salt is the chloride or hydrogen sulphate.

14. A process for the manufacture of polyene compounds containing a 3,7-dimethyl - nona - 1,3,5,7 - tetraen - 1 - yl group, substantially as hereinbefore described with reference to any one of the foregoing Examples.

15. Polyene compounds containing a 3,7-dimethyl - nona - 1,3,5,7 - tetraen - 1 - yl group, when manufactured by the process claimed in any one of claims 1 to 14 inclusive or by an obvious chemical equivalent thereof.

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